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Baseline Characteristics of the Fellow Eye in Patients with Neovascular Age-Related Macular Degeneration: Post Hoc Analysis of the VIEW Studies

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Key Words
Anti-VEGF agents · Best-corrected visual acuity · Bilateral disease · Choroidal neovascularization · Fellow eye · Intravitreal aflibercept · Neovascular age-related macular degeneration · Pooled analysis · Ranibizumab

Abstract

Purpose: The aim was to describe baseline characteristics of the fellow eye of patients with neovascular age-related macular degeneration (nAMD). ***Methods:*** A pooled, post hoc analysis of patients with nAMD enrolled in the VIEW studies was carried out. The VIEW studies compared intravitreal aflibercept (monthly or every 2 months after 3 monthly injections) with monthly ranibizumab. Baseline choroidal neovascularization (CNV) status of fellow eyes and baseline best-corrected visual acuity (BCVA) and lens status of all eyes were evaluated. Additional analyses evaluated the presence of drusen and pigment in fellow eyes. ***Results:*** When comparing both eyes, baseline BCVA was worse in 23.8% of fellow eyes and in 75.2% of study eyes. Lens status of fellow eyes and study eyes was similar. Baseline visual acuity of the study eye and that of the fellow eye were not correlated. Most fellow eyes had signs of early AMD, with 34.6% (n = 843) of fellow eyes having evidence of scarring. ***Conclusions:*** In patients in the VIEW studies, most fellow eyes had evidence of AMD, highlighting the importance of examining both eyes, with close follow-up thereafter, in order to detect and treat CNV earlier as needed.

Introduction

Neovascular age-related macular degeneration (nAMD) is a leading cause of vision loss and blindness among individuals aged >65 years in industrialized countries [1, 2]. Early therapies did not produce significant improvements in visual acuity (VA) [2]. The success of the first injectable anti-vascular endothelial growth factor (VEGF) agent, pegaptanib sodium, suggested that VEGF was driving the choroidal neovascularization (CNV) as-

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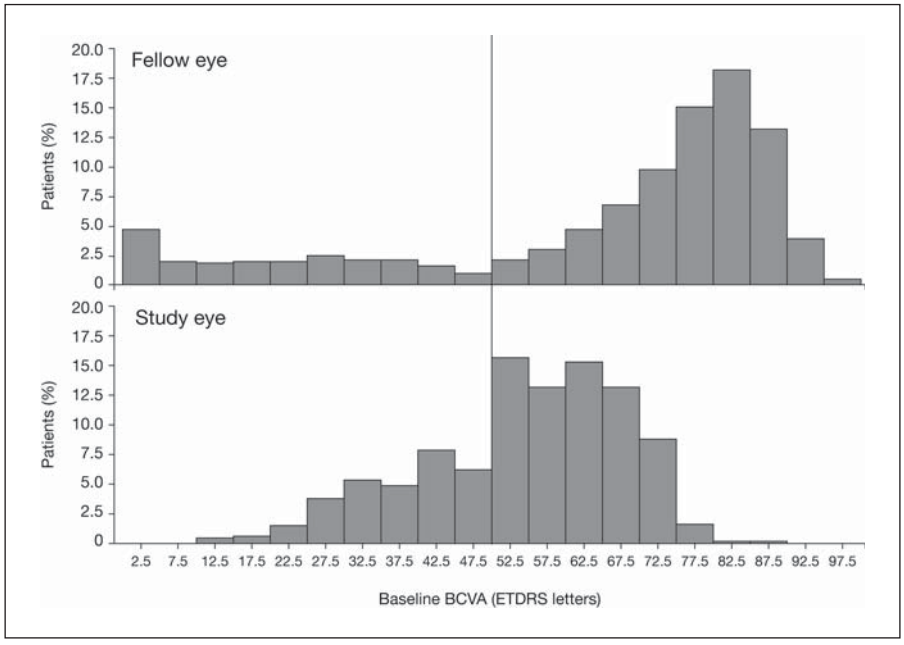

Fig. 1. Distribution of baseline BCVA for fellow eye (upper panel) and study eye (lower panel). ETDRS = Early Treatment Diabetic Retinopathy Study.

sociated with nAMD. Later, treatment with monthly ranibizumab was shown to prevent vision loss in most patients, and to meaningfully improve VA in about one third of patients [3, 4]; however, the potential risk of side effects plus the burden of monthly visits led to efforts to decrease injection and monitoring frequency [2].

Aflibercept, a recombinant fusion protein comprising key VEGF-binding domains of human VEGF receptors 1 and 2 fused to the Fc domain of human immunoglobulin G1, binds VEGF and placental growth factor, and demonstrated a higher binding affinity than ranibizumab or bevacizumab [5, 6] in preclinical studies, which could account for less frequent dosing. The VIEW studies compared intravitreal aflibercept injection, monthly or every 2 months after 3 initial monthly injections, with monthly ranibizumab. At week 52, all groups had similar visual, morphologic, and safety outcomes [2].

Previous reports have described the incidence of new CNV in the fellow eye during therapy. CNV in one eye of a patient with AMD is a strong risk factor for the development of CNV in the fellow eye (annual incidence: 4–19%) [7–9]. Although nAMD trials have reported increased rates of CNV development in fellow eyes during therapy, perhaps due to more careful monitoring during clinical studies [10, 11], information on baseline incidence of CNV in fellow eyes was not reported. Since early detection of CNV in the fellow eye may lead to better long-term visual outcomes, it may be important to characterize fellow eyes at baseline. The aim of this study was, therefore, to evaluate the baseline status of fellow eyes and to test the hypothesis that patients with worse VA in the fellow eye might present earlier, and with better VA in the study eye.

Methods

A pooled, post hoc analysis of patients enrolled in the VIEW studies was carried out in order to characterize the baseline status of fellow eyes, with a focus on baseline VA, lens status, and AMD-associated findings.

The VIEW studies (NCT00509795; NCT00637377) were randomized, double-masked, multicenter, parallel-group, active-controlled phase 3 trials that recruited >2,400 patients with treatment-naïve nAMD from >360 centers worldwide. The trials compared standard of care (monthly ranibizumab) with 3 dosing regimens (0.5 mg monthly, 2 mg monthly, 2 mg every other month following 3 initial monthly injections) of intravitreal aflibercept injection [2]. The VIEW study protocols were approved by the institutional review boards or ethics committees for each clinical site and all participants provided written informed consent.

In the original VIEW studies, for patients who met eligibility criteria in both eyes, the eye with the worse VA was selected as the study eye. In this post hoc analysis, 3 different sources within the VIEW database were compared. The Past Medical History and Adverse Event (PMH) data were used to search for previous diagnoses of CNV before baseline. The Prior and Concomitant medications data (CONMED) used CONMED codes for 'first use of ranibizumab (Lucentis®)/bevacizumab (Avastin®)/pegaptanib (Macugen®) in fellow eye before baseline' to search for first use of CNV medication. The Digital Angiography Reading Center (DARC) database

used 'Choroidal Neovascularization; Fellow Eye' to search for anatomic evidence of fellow eye CNV at baseline. Inclusion required the identification in ≥1 database. Baseline best-corrected VA (BCVA) and lens status were assessed for all eyes. Baseline evidence of current/prior CNV, presence of hard/soft drusen, presence of intermediate/large drusen, and presence/location of pigment were assessed for fellow eyes only. Geographic atrophy could not be evaluated.

Results

Patients

Baseline characteristics of fellow eyes versus study eyes were described for 2,412 patients from the VIEW studies.

Baseline BCVA: Study Eye versus Fellow Eye

The mean (standard deviation) BCVA was 65.2 (25.8) letters (~20/50) in fellow eyes versus 53.8 (13.6) letters (~20/80) in study eyes. Severe visual impairment [≤36 letters (~20/200)] was seen in 16.9% of fellow eyes versus 12.4% of study eyes. Note that in the VIEW studies, only eyes with a letter score of 25–75 letters could be selected as study eyes. BCVA >80 letters (~20/25) was seen in 33.2% of fellow eyes versus 0.2% of study eyes. Baseline BCVA was worse in fellow eyes in 23.8% of patients and in study eyes in 75.2% of patients (0.3% missing; 0.6% baseline VA equal in both eyes). Distribution of baseline BCVA is shown in figure 1.

Baseline Characteristics: Fellow Eye

Overall, 2.5% of fellow eyes had anti-VEGF use prior to the first study day. Most fellow eyes had signs of AMD at baseline. Baseline drusen and pigment characteristics were assessed; only 10.0% (n = 226) of fellow eyes did not have drusen and only 11.8% (n = 132/1,120; pigment information only available for VIEW 1) did not have pigment at baseline (table 1). Breakdown of VA in fellow eyes with/without CNV is shown in figure 2. At baseline, 843/2,412 patients (34.6%) presented with scarring (presence of fibrosis) as a sign of prior CNV. Of these 843, most (64.8%; n = 546) were categorized in >1 database as having CNV. Some patients were categorized as having CNV in only 1 database (16.1%; n = 136 categorized in DARC only, 19.0%; n = 161 categorized in PMH only). The lens status of fellow eyes was similar to that of study eyes; pseudophakia was seen in 34.3% (fellow eyes) and 38.0% (study eyes).

Baseline Study Eye VA versus Baseline Fellow Eye VA

We examined whether patients with worse fellow eye VA present earlier and with better VA in the study eye.

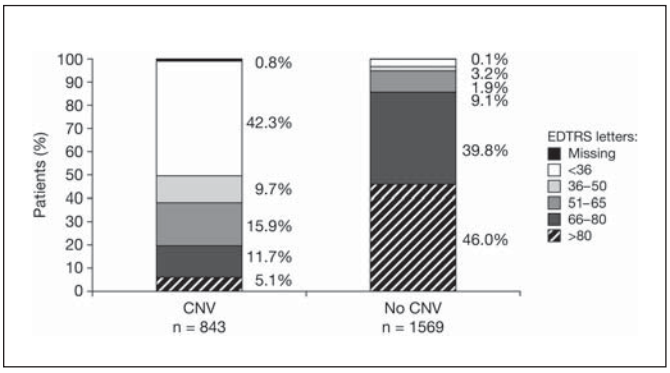

Fig. 2. Baseline BCVA and CNV in the fellow eye. ETDRS = Early Treatment Diabetic Retinopathy Study.

Table 1. Baseline drusen and pigment characteristics in fellow eyes

Drusen[a]	
Hard	2,011 (88.6)
Soft	1,693 (74.5)
None	226 (10.0)
Number of intermediate/large drusen[b] (n = 2,256)	
Not entered	102 (4.5)
0–5	1,124 (49.8)
6–10	255 (11.3)
11–20	259 (11.5)
>20	522 (23.1)
Pigment[c] (n = 1,120)	
Extrafoveal	985 (87.9)
Subfoveal	223 (19.9)
None	132 (11.8)

Figures are numbers with percentages in parentheses. Characteristics are not mutually exclusive. [a] Hard drusen have well-defined/distinct borders (usually small/intermediate); soft drusen have confluent/indistinct borders (usually intermediate/large). [b] Intermediate ≥63 to <125 μm; large ≥125 μm. [c] Information only available for VIEW 1 patients (n = 1,120).

The mean (SD) study eye VA was 53.7 (13.8) when the baseline fellow eye VA was ≥50 letters, and 54.0 (12.7) when the baseline fellow eye VA was <50 letters, confirming that our hypothesis was not supported.

Discussion

AMD is a bilateral disease, and risk of neovascularization in a fellow eye increases over time after initial diagnosis [12]. Hence, it is important to determine the status of both eyes at diagnosis. The current analysis showed

that most fellow eyes in the VIEW studies had signs of AMD at baseline, confirmed by the presence of drusen and pigment. Approximately one third of the fellow eyes also had evidence of CNV at baseline.

The average baseline condition of fellow eyes at the time these trials commenced may have been worse than the average baseline condition of fellow eyes today. Management of nAMD is constantly evolving with availability of new therapies and diagnostic tools, as well as ongoing evaluation of optimal dosing regimens. Historically, nAMD was treated with laser photocoagulation, which often caused a permanent loss of central vision. Earlier treatments that followed generally decreased severe vision loss with less damage to associated choroid and retina [13]. In the current study, ~35% of patients showed evidence of scarring. It was not until the early 2000s that VEGF inhibitors became available as treatment options for nAMD that stabilize or significantly improve VA. Questions remain about best dosing regimens, and efforts to minimize the burden of frequent injections sometimes result in undertreatment. As advanced therapies continue to be introduced and care of patients with nAMD progresses, it is expected that the prognosis for these patients will improve, resulting in better outcomes.

It can be speculated that if one eye already has suffered visual loss due to CNV, the second eye would be followed closely and changes would be noticeable early. Early diagnosis should lead to presenting vision in the second eye being better than that in the initial eye. However, this was not supported by the current analysis, which found no difference in baseline VA of study eyes as a function of baseline VA of fellow eyes.

This analysis was potentially limited by the fact that specific inclusion and exclusion criteria are imposed on patients enrolled in clinical trials, and this may introduce a selection bias. For example, for those patients who met eligibility criteria in both eyes, the eye with the worse VA was selected as the study eye. However, the better-seeing eye was selected as the study eye in 575/2,412 (23.8%) patients in VIEW 1 and 2; in these patients, the baseline BCVA score in the fellow eye was <25 letters in 294/575 (51.1%) patients; in the remaining 281/575 (48.9%) patients, other reasons were present not to select the worse eye as the study eye. Nevertheless, these patient populations may not truly reflect those seen in real-world clinical practice; this, and the resultant characterization of the patients in this analysis, should be taken into consideration when interpreting these results.

Conclusions

The risk of development of CNV in untreated eyes after diagnosis of the initial eyes has been well described; however, information on the prevalence of CNV in the second eye at the time of the initial diagnosis is scarce. In this first report describing baseline characteristics of fellow eyes using data from the VIEW study, most patients had evidence of AMD characteristics in fellow eyes at baseline, with one third presenting with signs of CNV. As AMD is a bilateral disease, it is important to evaluate the status of both eyes during clinical examination even if only 1 eye presents with CNV in order to be able to detect and treat early for optimal outcomes. Close follow-up is needed, as fellow eyes are at high risk of developing CNV in the near future.

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Disclosure Statement

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